



Non-alcoholic fatty liver disease in sub-Saharan Africa 1

Epidemiology, risk factors, social determinants of health, and current management for non-alcoholic fatty liver disease in sub-Saharan Africa

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Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease globally and is estimated to affect approximately 25% of the world's population. Data about the prevalence and incidence of NAFLD in Africa are scarce, but the prevalence is estimated to be 13·5% for the general population. This is likely to be an underestimate considering the increasing burden of non-communicable diseases, particularly the rising prevalence of obesity and type 2 diabetes, driven by the overlapping challenges of food insecurity, nutritional transition, and associated increased consumption of calorie-dense foods. Establishing the true prevalence of NAFLD, raising public awareness around the risk factors behind the increase in NAFLD, and proactively addressing all components of metabolic syndrome will be important to combat this silent epidemic, which will have long-term health-care costs and economic consequences for the region.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading global cause of chronic liver disease, estimated to affect approximately 25% of the world's population.¹ Data for the prevalence and incidence of NAFLD in Africa are scarce. A meta-analysis reported a NAFLD prevalence of 13·5% (95% CI 5·67–28·7), ranging from 9% in Nigeria to 20% in Sudan.^{1–3}

NAFLD, defined as the presence of more than 5% hepatic steatosis without causative factors such as alcohol, certain drugs, or other defined liver disorders, encompasses the histological spectrum of simple steatosis, non-alcoholic steatohepatitis (NASH), and advanced fibrosis. Overall, 3–5% of patients with NAFLD develop NASH, with 1–2% developing advanced fibrosis.^{1,2}

Extrahepatic manifestations of NAFLD include cardiovascular disease, cerebrovascular disease, chronic kidney disease, extrahepatic malignancies, polycystic ovary syndrome, and sleep apnoea.⁴ NASH with advanced hepatic fibrosis can rapidly progress to cirrhosis and decompensate with hepatic encephalopathy, ascites, variceal bleeding, and death.⁵ Although liver-related mortality is increased, cardiovascular disease remains the leading cause of death in patients with NAFLD and liver fibrosis stages F3 or F4.⁶

NAFLD is seldom considered as a complication of metabolic syndrome, despite its increasing prevalence and associated morbidity and mortality with long-term health-care costs and consequent economic burden.^{4,7,8} NAFLD is more likely to be diagnosed incidentally, as specific screening is seldom recommended in clinical management guidelines for obesity, diabetes, dyslipidaemia, and hypertension. The risk of hepatocellular carcinoma, which can occur in the absence of cirrhosis,

is underestimated. Determining a more precise prevalence of NAFLD and associated disorders, and in turn addressing the disease burden in sub-Saharan Africa, will require increased awareness and access to affordable, reliable diagnostic tests.

The burden of non-communicable diseases associated with NAFLD in sub-Saharan Africa

A transition from the infectious diseases of tuberculosis, malaria, and HIV to an increasing burden of non-communicable diseases (NCDs) is occurring in sub-Saharan Africa.⁹ According to the 2017 Global Burden of Disease (GBD) study, the all-age total disability-adjusted life-years (DALYs) due to NCDs increased by 67% between 1990 (90·6 million; 95% uncertainty interval 81·0–101·9) and 2017 (151·3 million; 133·4–171·8). This increase reflected a rise in the proportion of total DALYs attributable to NCDs, from 18·6% (17·1–20·4) to 29·8% (27·6–32·0). Cardiovascular diseases were the second leading cause of NCD burden in 2017, resulting in 22·9 million DALYs (21·5–24·3), which is 15·1% of the total NCD burden.⁹ In southern sub-Saharan Africa, diabetes and kidney disease were particularly onerous, with the crude rate of 1927·2 DALYs per 100 000 population (1693·8–2191·9) being almost twice that of other sub-Saharan African regions (1233·3 DALYs per 100 000 population [1047·6–1432·8] in central, 887·4 [771·0–1016·7] in western, and 915·2 [811·3–1029·2] in eastern sub-Saharan Africa).⁹ Africans with NCDs are younger by 10 years or more compared with people in other world regions.¹⁰ Thus, it is anticipated that sub-Saharan Africa will experience the largest global increase in NCD-related mortality.¹¹

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This is the first in a **Series** of two papers on non-alcoholic fatty liver disease in sub-Saharan Africa

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Metabolic syndrome

Metabolic syndrome is core to NCDs and the development of NAFLD. An individual with metabolic syndrome is three times more likely to have a cardiovascular or cerebrovascular event and twice as likely to die from that event as an individual without metabolic syndrome.¹² A systematic review and meta-analysis¹² of 65 studies in 14 different countries, including 34 324 healthy participants aged 16 years or older, reported a pooled prevalence of metabolic syndrome in sub-Saharan Africa ranging from 11.1% to 23.9% depending on various diagnostic criteria used. The prevalence of metabolic syndrome in sub-Saharan Africa was higher in women than in men and tended towards being greater in semi-urban and urban areas than in rural areas. Prevalence of metabolic syndrome was highest in southern Africa, consistent with the higher rates of obesity there, followed by eastern, western, and central Africa.^{12,13}

Obesity

WHO defines overweight as BMI 25 kg/m² or higher, and obesity as BMI 30 kg/m² or higher.¹⁴ A 2017 study revealed that between 1980 and 2014, the age-standardised body-mass index (BMI) in sub-Saharan Africa increased from 21.0 kg/m² (95% credible interval [CrI] 20.3–21.7) to 23.0 kg/m² (22.7–23.3) in men, and from 21.9 kg/m² (21.3–22.5) to 24.9 kg/m² (24.6–25.1) in women.¹³ Particularly concerning is the increasing prevalence of overweight and obesity in children, with a systematic review showing a transition towards overweight and obesity among school-aged children and youth in sub-Saharan Africa. In children, the weighted average of overweight and obesity was 10.6% and that of obesity alone was 2.5%, being higher in girls, individuals living in urban areas, and individuals of higher socioeconomic status.^{13,15}

Diabetes

Between 2017 and 2045, Africa is projected to experience the highest relative increase worldwide in diabetes: the number of adults with all types of diabetes is predicted to increase from 16 million to 41 million people, a 156% increase.¹⁶ Between 1980 and 2014, the age-standardised prevalence of diabetes increased from 3.4% (95% CrI 1.5–6.3) to 8.5% (6.5–10.8) in men and from 4.1% (2.0–7.5) to 8.9% (6.9–11.2) in women. A positive association (correlation coefficient approximately 0.9) was observed between mean BMI and diabetes prevalence in 1980 and 2014.¹³ A 2020 meta-analysis reported an average pooled prevalence of undiagnosed diabetes among adults in Africa of 3.85% (95% CI 3.10–4.60) and in the different regions: 4.72% (2.64–6.80) in western, 4.43% (3.12–5.74) in eastern, 4.27% (1.77–6.76) in northern, and 1.46% (0.57–2.34) in southern Africa.¹⁷ NAFLD prevalence in patients with type 2 diabetes in Africa, based on four studies, was 30.39% (11.64–67.09).¹⁸

Hypertension

A systematic review and meta-analysis of 33 studies done in sub-Saharan Africa (110 414 participants, mean age 40 years) assessing the burden of hypertension between 2000 and 2013 confirmed a pooled prevalence of 30% (95% CI 27–34). 18% (14–22) were receiving treatment and blood pressure control was attained in 7% (5–8).¹⁹

Dyslipidaemia

In a 2018 systematic review of 177 population-based studies with 294 063 participants, the pooled prevalence of dyslipidaemia, a leading contributor to cardiovascular disease, was 25.5% (95% CI 20.0–31.4) in the general African population.²⁰ Detection and effective treatment of dyslipidaemia is important to reduce the risk of NAFLD and reduce cardiovascular diseases in Africa.

Chronic kidney disease

A meta-analysis of 98 studies involving 98 432 individuals reported an overall prevalence of 15.8% (95% CI 12.1–19.9) of chronic kidney disease stages 1 to 5 and a 4.6% (3.3–6.1) prevalence of chronic kidney disease stages 3 to 5 for the general population in Africa.²¹ A cross-sectional population-based study suggested that the increasing incidence of hypertension, HIV, and diabetes in Africa were all independently associated with chronic kidney disease.²²

Risk factors and prognostic indicators for NAFLD

NAFLD is the liver manifestation of metabolic syndrome and is part of a multisystem disease.⁴ The relationship between NAFLD and metabolic syndrome has been consolidated by the proposal to amend the nomenclature for NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD). The definition of MAFLD is based on the presence of hepatic steatosis with at least one of the following: overweight, obesity, type 2 diabetes, or metabolic disease. MAFLD is not a diagnosis of exclusion.²³ Nevertheless, the pathogenesis of NAFLD involves a complex interplay between genetics, epigenetics (gut microbiome), and environmental triggers, with obesity and type 2 diabetes being the predominant modulators of NAFLD and NASH.^{2,6,24,25}

Clinical predictors of NASH and fibrosis include male sex, elevated aminotransferases, type 2 diabetes, age older than 50 years, Hispanic ethnicity, and having a first-degree relative with advanced NAFLD fibrosis.^{26,27} The risk of advanced fibrosis was 12-times higher in first-degree relatives of individuals with NAFLD cirrhosis, after adjusting for age, sex, BMI, type 2 diabetes, and Hispanic ethnicity.²⁸ An increasing number of metabolic diseases are associated with increased risk of progressive liver disease and reduced survival.^{26,27} The odds ratios for the development of moderate-to-severe fibrosis for metabolic risk factors are 1.61 (95% CI 1.21–2.01; *p*=0.0374) for hypertension, 1.64 (1.13–2.17; *p*=0.0258) for type 2

diabetes, 1.69 (1.11–2.28; $p=0.0246$) for type 2 diabetes and hypertension, and 1.72 (1.13–2.31; $p=0.0205$) for type 2 diabetes, hypertension, and visceral obesity.²⁷

Obesity

Obesity is associated with a 3.5-times increased risk of NAFLD.²⁹ There is a dose-dependent relationship between BMI and NAFLD risk (per one-unit increment in BMI, relative risk 1.20, 95% CI 1.14–1.26, $p<0.001$).³⁰ Visceral adiposity and its surrogate marker, waist circumference, is a key risk factor for many complications of metabolic syndrome and has a stronger association with NAFLD than does BMI alone, predisposing to a greater risk of NASH and fibrosis.³¹ Both BMI and waist circumference should be measured to assess the risk and progression of NAFLD. Increased visceral adiposity is a risk factor in the development of NAFLD in lean individuals (ie, BMI <25 kg/m²), especially in Asian populations (in whom lean BMI is <23 kg/m²),^{2,32} with the *PNPLA3* I148M allele playing a contributing role.³³

Type 2 diabetes

The relationship between NAFLD and type 2 diabetes is bidirectional. The global prevalence of NAFLD in patients with type 2 diabetes, based on ultrasound or proton magnetic resonance spectroscopy, is 55.48% (95% CI 47.26–63.67).¹⁸ NAFLD is associated with a roughly 2.2-fold increased risk of incident diabetes, with risk paralleling the underlying NAFLD severity.³⁴ Type 2 diabetes accelerates the progression of liver disease in NAFLD and is a predictor of advanced fibrosis and mortality.^{2,34} The global prevalence of NASH among individuals with type 2 diabetes is 37.3% (95% CI 24.7–50.0), with advanced fibrosis occurring in 17.0% (7.2–34.8) of patients with NAFLD and type 2 diabetes.³⁵

Dyslipidaemia

The global pooled dyslipidaemia prevalence estimates are 69.2% (95% CI 49.9–83.5) in patients with NAFLD and 72.1% (54.6–84.8) in patients with NASH.¹ The pooled overall prevalence estimates for hypertriglyceridaemia are 40.7% (30.8–51.5) in patients with NAFLD and 83.3% (36.87–97.72) in patients with NASH.¹ Ratios of high total cholesterol to HDL cholesterol and high triglyceride to HDL cholesterol are associated with increased risk of advanced NAFLD.³⁶

Polycystic ovary syndrome

Polycystic ovary syndrome is associated with insulin resistance and metabolic syndrome, and affects about 10% of the female population. This is a high-risk group for the development of NAFLD and NASH.³⁷

Gut microbiome

The gastrointestinal tract and the gut microbiome composition play a role in the development of NAFLD.

Clinical studies have shown that NAFLD is associated with dysbiosis, characterised by increased growth of bacteria such as Enterobacteriaceae and *Escherichia coli*, and a decrease in *Faecalibacterium prausnitzii*. Intestinal dysbiosis and microbiome instability influenced by the consumption of saturated fatty acids, fructose, and advanced glycated end-products contribute to development of liver disease. Dysbiosis is associated with altered production of short-chain fatty acids; altered choline and bile acid metabolism; increased lipopolysaccharide-containing bacteria and bacteria-derived ethanol; increased intestinal permeability; and promotion of chronic low-grade inflammation with induction of pro-inflammatory cytokines (IL-1, IL-6, and TNF α), activation of hepatic TLR4, and generation of reactive oxygen species. All of these are contributing factors to the development of NAFLD.^{4,38}

Epidemiology of NAFLD in sub-Saharan Africa

Sub-Saharan Africa, a middle-to-lower-income region, has varied evolving economies and increasing urbanisation. The effect is pro-NAFLD dietary and behavioural changes, including a move towards a more sedentary, urban lifestyle. In food-insecure countries (ie, countries in which individuals lack regular access to enough safe and nutritious food for normal growth and development and an active and healthy life), transition to an increased use of inexpensive, low nutritional value, higher calorie options drives obesity and metabolic syndrome. Given this issue, WHO and the UN General Assembly have identified food insecurity as a global health risk because it promotes poor metabolic health.^{39,40} A meta-analysis focusing on the relationship between food insecurity and metabolic risk factors in sub-Saharan Africa corroborates a high pooled prevalence estimate of key metabolic risk factors among food-insecure participants (41.8% [95% CI 33.2–50.8, $I^2=99.5\%$]).⁴¹ The most prevalent risk factors were dyslipidaemia (27.6% [6.5–54.9]), hypertension (24.7% [15.6–35.1]), and overweight (15.8% [10.6–21.7]).⁴¹ Reliable data about prevalence and incidence of NAFLD in sub-Saharan Africa are lacking.⁶ Estimates based on GBD data (1990–2017) suggested that the age-standardised prevalence of NAFLD in sub-Saharan Africa ranged from 5.0–7.5% to 10.1–12.5%, with 20.1–25.0% in Mauritius. Ghana and Benin had the highest estimated annual percentage change of 1.26–1.5.⁴²

Western sub-Saharan Africa

Regional data about the incidence of NAFLD in western sub-Saharan Africa are scant. Using data derived from the GBD study, NAFLD cases have increased from 8.4 per million in 1990 to 23.2 per million in 2017, with the age-standardised prevalence increasing from 6.5% to 8.0%.⁴² This yields an estimated annual percentage change in age-standardised prevalence from 1990 to 2017 of 0.69 (95% CI 0.63–0.75).⁴² NAFLD risk factors, including obesity and type 2

diabetes, are increasing in the region.^{43–46} In Nigeria, NAFLD prevalence has been reported as 9.5–16.7% in people with type 2 diabetes and 1.2–4.5% in people without diabetes.^{45,47} NAFLD was associated with central obesity (waist circumference >88 cm in women and >102 cm in men) and dyslipidaemia.⁴⁵

In Ghana, obesity prevalence has increased from 5.5% to 25.4% in the past decade, with a rising NAFLD incidence being a potential consequence of this.^{48,49} A Ghanaian cross-sectional study of 88 premenopausal and 97 postmenopausal women⁵⁰ revealed an overall prevalence of metabolic syndrome of 25% (46 of 185 women) and NAFLD prevalence of 40% (74 of 185 women). Among postmenopausal women, metabolic syndrome prevalence was 33% (32 of 97 women) and NAFLD prevalence was 49% (48 of 97 women), higher than the 16% prevalence of metabolic syndrome (14 of 88) and 30% prevalence of NAFLD (26 of 88) observed in premenopausal women.⁵⁰ Coronary artery disease and comorbidities of metabolic syndrome and NAFLD, were significantly correlated (odds ratio 5.2, 95% CI 2.2–12.4; $p < 0.001$).⁵⁰ An ultrasound-based study of 97 patients undergoing elective general and gynaecological procedures found that 54 (56%) had features of NAFLD, with associated prolonged hospital stay.⁵¹

Central sub-Saharan Africa

In central sub-Saharan Africa, GBD estimates noted NAFLD cases increasing from 2.3 per million in 1990 to 6.2 per million in 2017, with age-standardised prevalence increasing from 6.5% to 7.5%.⁴² The estimated annual percentage change in age-standardised prevalence from 1990 to 2017 was 0.58 (0.50–0.67).⁴² In urban-based individuals with metabolic syndrome, high NAFLD prevalences have been documented: 37.2% in Burundi and 38.7% in Congo (Brazzaville).^{52,53}

Obesity is less prevalent in the central African region than in other regions. For example, the proportion of individuals with BMI 30 kg/m² or higher in Equatorial Guinea is 17.5% (world ranking 119); in Cameroon, 11.4% (135); in Congo (Brazzaville), 11.0% (136); in DR Congo, 6.7% (177); in Chad, 6.1% (178); in Rwanda, 5.8% (180); and in Burundi, 5.4% (186).⁵³ However, obesity prevalence has increased progressively over the past two decades. For example, in Burundi it has increased from 2.6% to 5.4% and in DR Congo it has increased from 4.4 to 6.7%.⁵⁴ This trend relates to lifestyle changes mostly in the urban middle classes.⁵⁵ Notably, the traditional local diet appears to be protective, with foresters (more vegetarian diet) and the Sahelians (more meat-based diet) having a lower prevalence of obesity.⁵⁵

NAFLD risk factors such as diabetes are increasing in prevalence in central Africa; for example, in Cameroon, age-standardised prevalence of diabetes increased from 2% in 1999 to 5.8% in 2018.¹³ This finding could suggest an epidemiological transition, with NAFLD emerging at greater rates over time.

Southern sub-Saharan Africa

Estimates using GBD data show that NAFLD cases have increased from 3.7 per million in 1990 to 8.1 per million in 2017, with the age-standardised prevalence increasing from 9.3% to 11.4%.⁴² This gives an estimated annual percentage change in age-standardised prevalence of 0.73 (95% CI 0.69–0.77) during this period.⁴² Risk factors such as diabetes and obesity are invariably surrogate markers of the potential NAFLD burden. Across all countries in southern sub-Saharan Africa, the age-standardised prevalence of diabetes increased between 1980 and 2014.⁵⁶ For example, in Botswana in 1980, diabetes prevalence was 2% in men and 3.8% in women, increasing to 7.6% in men and 9.5% in women in 2014. Similarly, in South Africa, the prevalence increased from 4.8% in men and 7.7% in women in 1980, to 9.7% in men and 12.6% in women in 2014.⁵⁶

Obesity rates in southern sub-Saharan Africa are the highest in sub-Saharan Africa. Age-standardised obesity estimates are 11.7% in men and 37.0% in women, and combined estimates of obesity and overweight are 34.2% in men and 63.7% in women.⁵⁷ Botswana and South Africa are most affected, with 26.5–38.6% of men and 50.7–64.0% of women being overweight, and 7.0–14.5% of men and 25.5–38.5% of women being obese, in 2016.⁵⁸ Malawi and Madagascar are only marginally affected, probably reflecting differing socioeconomic levels.⁵⁸ A South African NAFLD study among overweight or obese adults attending a liver clinic evaluated liver biopsies of 127 patients.⁵⁹ The prevalence of NAFLD was 87% ($n=111$), simple steatosis was 51% ($n=65$), NASH was 36% ($n=46$), and advanced liver fibrosis was 17% ($n=20$). All patients with NAFLD had insulin resistance, but only 5% of patients were Black, the majority being either of mixed ancestry or White.⁵⁹

Of note, HIV infection and its therapies and metabolic consequences are potential additive factors that might affect NAFLD prevalence in southern sub-Saharan Africa, the region with the highest HIV prevalence globally.⁶⁰ Retrospective data of liver biopsies in a South African study showed liver steatosis was more frequent in HIV-positive patients (23 [21%] of 108) compared with HIV-negative patients (three [12%] of 25).⁶¹ A prospective study of 301 HIV-positive patients undergoing a liver biopsy reported NAFLD in 58 (19%) patients, of whom 16 (28%) had steatohepatitis.⁶²

Eastern sub-Saharan Africa

Using GBD data, estimates for NAFLD cases increased from 7.1 per million in 1990 to 18.0 per million in 2017, with age-standardised prevalence increasing from 6.0% to 7.0%.⁴² The estimated annual percentage change in age-standardised prevalence in this time period was 0.58 (95% CI 0.55–0.60).⁴² Data from the GBD study showed rising diabetes trends, with incident cases of 314 000 in 1990 increasing to 726 000 in 2017, with an estimated annual percentage change in incident cases of 0.25.⁶³

Ethiopia was estimated to have 2.6 million people (95% CI 1.1–3.8) with diabetes in 2017.^{15,64} Prevalence of diabetes in adults aged 35 years or older in a cross-sectional population-based survey in northwest Ethiopia was 5.1% (95% CI 3.8–6.4) for urban dwellers and 2.1% (1.2–2.9) for rural dwellers.⁶⁵ In a 2020 systematic review and meta-analysis of 16 studies and 19 527 participants, the estimated pooled prevalence of overweight in adult Ethiopians was 19% and that of obesity was 5.4%.⁶⁶ There is regional variation in Ethiopia; the prevalence of overweight varied from 16.1% to 25.3%, and that of obesity from 5.6% to 16.2%.^{67–70} A cross-sectional study from southeast Ethiopia found a prevalence of NAFLD of 73% (70 of 96 people) in those with type 2 diabetes.⁷¹ In an unmatched case-control study among patients attending a hepatology and gastroenterology clinic in Addis Ababa, 163 (20%) of 812 patients with chronic liver disease had NAFLD and 192 (24%) of 798 without chronic liver disease had NAFLD.⁷² NCDs in Ethiopia were the leading contributors to age-standardised death rates in 2015, with 711 deaths per 100 000 people (95% uncertainty interval 468.8–1036.2). Metabolic risk factors included high rates of hypertension (16%), hyperglycaemia (5.9%), hypercholesterolaemia (5.6%), overweight (5.2%), and obesity (1.2%).⁷³

A 2014 population-based NAFLD study suggested a prevalence of 20% in the Sudanese population.⁷⁴ A subsequent cross-sectional hospital-based study revealed an overall NAFLD prevalence of 50% (84 of 167) in individuals with diabetes, with overweight, obesity, visceral obesity, and dyslipidaemia being significantly associated with NAFLD; having two to three metabolic syndrome components was associated with a higher prevalence of NAFLD (12% NAFLD prevalence among patients with two components and 21% among those with three components).⁷⁵ In a population-based urban study in north Sudan, the overall prevalence of diabetes was 19.1% (182 of 954 people) and impaired glucose tolerance 9.5% (91 of 954 people).⁷⁶ A study among rural communities of north Sudan has shown that the prevalence of undiagnosed diabetes was 2.6% (29 of 1111 people) and impaired glucose tolerance 1.3% (14 of 1111 people).⁷⁷

An analysis of healthy Black Africans from a global study to determine reference intervals found a metabolic syndrome prevalence of 25.6% (95% CI 22.0–29.5) in urban Kenyans.⁷⁸

Overall, the reported NAFLD prevalence is probably an underestimate, as the burden of NCDs and rising prevalence of overweight and obesity and diabetes in eastern sub-Saharan Africa suggest NAFLD is likely to be more prevalent.

Social and other determinants of NAFLD in sub-Saharan Africa

A complete understanding of the drivers of NAFLD in sub-Saharan Africa is required to enable an appropriate response to the growing problem. Many factors,

including variability in dietary composition, exercise and lifestyle habits, environmental factors, and genetics, can influence the burden of NAFLD in the region. Many sub-Saharan African countries are undergoing rapid but variable epidemiological transitions driven by fast urbanisation; 41.3% of the population were living in urban areas in 2020 compared with 27.4% in 1990.⁷⁹ The importance of changes in nutrient intake and their effect on the development of obesity and type 2 diabetes are known. Factors influencing nutrition transition in Africa include food insecurity, urbanisation, and economic growth with increases in income and globalisation.^{41,80,81} Gross domestic product in many sub-Saharan African countries has progressively increased, while the UN Food and Agriculture Organisation has shown a steady increase in daily caloric intake in Africa as a consequence of the nutritional transition.⁸² Traditional diets, which are high in fibre and low in fat, are being substituted by more calorie-dense diets with increased intake of sugar-sweetened beverages and fast foods and increased fat and protein consumption.^{38,80,81}

Obesity and type 2 diabetes have been associated with soft drink consumption, and soft drink intake is often higher in patients with NAFLD than in those without NAFLD.^{83–85} Globally, consumption of sugar-sweetened beverages is increasing, especially in low-income and middle-income countries, including in sub-Saharan Africa.⁸⁴ People in some sub-Saharan African countries, such as South Africa, have considerably higher intake of sugar-sweetened beverages, correlating with the highest obesity prevalence in sub-Saharan Africa.^{85,86} The addition of fructose or sucrose to beverages and foods contributes to NAFLD development through increasing liver triglyceride synthesis. Data from mouse models suggest that fructose might promote hepatic triglyceride synthesis and NAFLD by damaging the intestinal barrier and promoting endotoxaemia; the endotoxin interacts with TLR4, triggering TNF α production by liver macrophages and thereby inducing lipogenic enzymes.⁸⁷

Small observational studies show an association between physical inactivity and NAFLD, suggesting that sedentary behaviour increases susceptibility to NAFLD and might be causative.⁸⁸ Moreover, reduced physical activity can increase the risk of NASH and fibrosis among patients with proven NAFLD.⁸⁹ Reduced physical activity, poor aerobic fitness, and overweight and obesity all contribute to hepatic insulin resistance, reduced mitochondrial function and triglyceride export, and increased de-novo lipogenesis and fatty acid uptake, leading collectively to increased hepatic lipid accumulation.⁸⁸ A meta-analysis including 28 randomised controlled trials showed that exercise, independent of diet, significantly reduces alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic triglyceride content.⁹⁰

In an individual participant data meta-analysis across ten sub-Saharan Africa countries (26 022 participants),

18.9% (95% CI 14.3–24.1; $I^2=99.0\%$) of adults (≥ 18 years) participated in leisure-time physical activity. Men were more likely to participate in leisure-time physical activity than women (risk ratio [RR] for women 0.43, 95% CI 0.32–0.60; $p<0.001$; $I^2=97.5\%$), with age inversely associated with participation. Higher levels of education were associated with increased participation in leisure-time physical activity (RR 1.30, 95% CI 1.09–1.55; $p=0.004$; $I^2=98.1\%$), with people living in rural areas or self-employed being less likely to participate. These associations remained after adjusting for time spent physically active at work or through active travel.⁹¹

It is increasingly recognised that genetic factors might account for the high NAFLD prevalence in some populations. Ethnic variation in NAFLD has been described, with a lower prevalence reported in people of African descent.⁹² Although the lower prevalence might be accounted for to some extent by under-recognition, genetic factors also play a role.⁹³ A number of candidate genes have been linked with NAFLD, including *PNPLA3*, *MBOAT7*, and *TM6SF2*.⁹⁴ The *PNPLA3* rs738409 C→G single nucleotide polymorphism has been shown to be independently associated with NAFLD and an increased risk of hepatocellular carcinoma in patients with cirrhosis.⁹⁵ The prevalence of this mutation differs among ethnic groups, with the lowest expression among African Americans, in whom a protective *PNPLA3* allele, rs6006460 G→T, was found to be common.⁹⁶

Subcutaneous fat stores might in fact be protective. In a South African study of 106 female volunteers, Black African women had a lower hepatic fat content on liver CT scan than their Indian and White counterparts, despite having a higher level of total body fat, subcutaneous body fat, BMI, and waist circumference. Subcutaneous fat was found to be a significant negative determinant of hepatic fat content.⁹⁷

There are no genetic studies of NAFLD from sub-Saharan Africa and a crucial need exists to better understand the risk of NAFLD in the region, as well as highlighting the risk factors for disease progression.

Management of NAFLD

In sub-Saharan Africa, the management of NAFLD must be centred on prevention. Irrespective of the scarce data available, specifically about NASH in sub-Saharan Africa, metabolic factors promoting NAFLD are abundantly present, with an increasing incidence on the continent. Sub-Saharan Africa is in a unique position to potentially offset the emerging NAFLD burden through aggressively pursuing prevention and primary care strategies. Management requires a diagnosis in the first instance and screening for NAFLD. Using a simple, non-invasive, cost-effective test such as the Fibrosis-4 (FIB-4) index would be of value in resource-constrained countries in targeted populations, such as people with obesity or type 2 diabetes.⁴³ Coupling FIB-4 with transient elastography for

the diagnosis of fibrosis, and with the controlled attenuation parameter of FibroScan for steatosis, can optimise performance, with cost being a limiting factor to access and availability.^{6,43}

General management strategies for NAFLD

Alcohol consumption

For a NAFLD diagnosis, alcohol consumption greater than 20 g/day for women and 30 g/day for men requires exclusion.⁹⁸ However, the effect of moderate amounts of alcohol use (<30 g/day) in the general population is conflicting. There are cardiovascular and metabolic benefits of moderate alcohol consumption that might be offset by the risks of cancer-related mortality and all-cause mortality.⁹⁹ Long-term moderate alcohol consumption data for people with metabolic cofactors suggested that alcohol was a major factor in promoting liver disease, even when average alcohol consumption was within the limits currently defined for NAFLD.¹⁰⁰ Overall, moderate alcohol consumption has been associated with a reduction in overall mortality, mostly accounted for by cardiovascular mortality benefits. However, no protective benefit has yet been conclusively shown in people with NAFLD.¹⁰¹ Another aspect of alcohol consumption relevant to NAFLD is the negative caloric effects of alcohol on diet and weight loss. Thus, alcohol abstinence remains the recommended advice for patients with NAFLD.

Lifestyle changes, dietary intervention, weight loss, and physical activity

Diet, as part of lifestyle changes, is key in NAFLD treatment. It has the strongest association with improved outcomes of all interventions and improves histology in NASH. A decreased caloric intake and reductions of at least 5% of bodyweight achieve a significant reduction in intrahepatic lipid content with a reduction in NAFLD activity scores.¹⁰² A meta-analysis of eight studies showed that weight loss of 7% or more was associated with improved NAFLD activity scores, while a prospective paired liver biopsy study of 261 patients found that 10% bodyweight reduction produced complete resolution of NASH in 26 (90%) of 29 patients.^{103,104} In essence, a 7–10% or greater reduction in bodyweight is associated with improvement in all NASH histological parameters, with at least one stage reduction in fibrosis; furthermore, cardiovascular and type 2 diabetes risks also decrease.¹⁰⁵

This weight reduction can only be achieved with a calorically restricted diet of 500–1000 kcal/day or a total intake of 1200–1800 kcal/day, low in fat and carbohydrates and rich in fibre, to effect 500 g to 1 kg weight loss per week. Data from analysis of the PIVENS and FLINT trials¹⁰⁵ of adults with NASH, in which paired liver biopsies were done, clearly showed that weight loss was associated with beneficial changes in both liver enzymes and NASH histology scores. Each kilogram of weight loss was associated with a 7% increase in odds of NASH resolution (95% CI 3–10; $p<0.001$), with no deterioration

in fibrosis. There was a 5% (95% CI 1–8; $p=0.01$) increase in likelihood of fibrosis improvement.¹⁰⁵ Dietary intervention and weight loss not only have clear benefits for NASH but also have cardiovascular, diabetes-related, and overall health advantages. With the rising obesity pandemic globally, it is self-evident that public health measures in sub-Saharan Africa need to target the prevention of weight gain while strongly supporting weight loss.

The role of sugar-sweetened beverages in promoting obesity, type 2 diabetes, and thus NAFLD risk is substantial, and it is advisable that population-wide interventions are introduced to reduce consumption of sugar-sweetened beverages in sub-Saharan Africa.

Exercise improves cardiovascular comorbidities, insulin-resistance, and hepatic triglyceride content. The general consensus is that exercise should be prescribed for 150–200 minutes per week in three to five sessions of moderate-intensity aerobic and resistance exercise.¹⁰² A systematic review showed that resistance exercise improves NAFLD with lower energy consumption. This is a useful intervention in patients with NAFLD who have impaired cardiorespiratory fitness or are unable to do aerobic exercise.¹⁰⁶ Exercise at sustained levels is also beneficial in maintaining weight loss.¹⁰⁷

Vitamin E

Vitamin E is an antioxidant that has been extensively studied for NAFLD, although there are few data from randomised controlled trials of vitamin E alone for NASH. The landmark PIVENS study showed that vitamin E reduced inflammation and steatosis but not fibrosis in patients with NASH without cirrhosis or diabetes.¹⁰⁸ In patients with diabetes, there was no improvement in inflammation or fibrosis. A 2021 systematic review and meta-analysis of eight studies concluded that vitamin E significantly reduced ALT and AST and improved liver pathology in all histological parameters, as well as lowering LDL cholesterol, fasting blood glucose, and serum leptin values.¹⁰⁹ Other data have indicated a benefit of vitamin E in patients with advanced fibrosis or cirrhosis (in both those with diabetes and those without diabetes) and improved transplant-free survival.¹¹⁰ Concerns have been raised regarding long-term vitamin E treatment and higher all-cause mortality, risk of haemorrhagic stroke, and risk of prostate cancer in men aged 50 years or older, but were not noted in this study.¹¹⁰

Managing the comorbidities of NAFLD

Type 2 diabetes

Appropriate glycaemic control is associated with a reduction in steatosis, a decrease in serum aminotransferases, and improvement of liver inflammation and fibrosis. Achieving glycaemic control requires appropriate use of anti-diabetic therapies. In sub-Saharan Africa, choice of appropriate anti-diabetic therapies is incumbent upon patient requirements as well as drug

availability, access to glycaemic monitoring, and laboratory or point-of-care HbA_{1c} testing. All of these factors are essential to achieving glycaemic control.

Specific anti-diabetic drugs might have potential effectiveness in NAFLD, beyond their glycaemic effect. Metformin, while improving HbA_{1c}, also has some modest weight loss benefits.¹¹¹ The data are not supportive with regard to histological improvement in NAFLD, but metformin might have an effect on reducing the incidence of hepatocellular carcinoma.¹¹² Given the absence of supportive data showing significant histological improvement, metformin is not currently recommended for treatment of liver disease in patients with NAFLD. Metformin remains an important, cost-effective therapy in sub-Saharan Africa for type 2 diabetes, although lifestyle modifications are required for maximum benefit.^{37,113}

The thiazolidinediones, including rosiglitazone and pioglitazone, have been extensively studied for the treatment of NASH. In a meta-analysis of eight randomised controlled trials, use of pioglitazone improved advanced fibrosis in NASH, including in individuals without diabetes.¹¹⁴ However, these drugs cause weight gain, oedema, osteoporosis, and bone fractures, especially in post-menopausal women.¹¹⁵ Additionally, these medications have been associated with an increased risk of cardiovascular events and possibly bladder cancer.¹¹⁶

Other anti-diabetic drugs have been associated with potentially beneficial effects in NAFLD. Liraglutide, a GLP-1 agonist, has shown significant improvement in glycaemic control and a reduction in cardiovascular events and deaths in people with diabetes.¹¹⁷ In a small study, liraglutide was associated with a significant improvement in NASH histology (reduced progression of fibrosis), ALT improvement, and weight loss.¹¹⁸ Semaglutide administered subcutaneously daily in a phase 2 placebo-controlled trial resulted in a significantly greater resolution of NASH than placebo, with no benefit on fibrosis observed.¹¹⁹ Weight loss was another observation, and was corroborated in a once-weekly dosing regimen of 2.4 mg yielding significant, sustained, and clinically relevant reduction in weight in overweight or obese participants, in both individuals without diabetes and those with diabetes.^{120,121}

Data about the effects of DPP-4 inhibitors in NAFLD are conflicting. Data from mouse models support these agents in preventing NASH-related liver fibrosis and development of hepatocellular carcinoma, independent of benefits for diabetes.¹²² However, clinical data suggest that DPP-4 inhibitors do not improve histological features of NAFLD or NASH, despite clear improvements in HbA_{1c} and liver enzymes.¹²³ SGLT2 inhibitors have renoprotective and cardioprotective benefits. Similar to DPP-4 inhibitors, mouse data for SGLT2 inhibitors and NAFLD improvement are supportive, but data in patients with NAFLD are scant.¹²⁴ Liver aminotransferases improve, as does glycaemic control, but liver histological

Search strategy and selection criteria

References for this paper were identified through searches of PubMed with the search terms “non-alcoholic fatty liver disease”, “NAFLD”, “non-communicable diseases”, “risk factors”, “epidemiology”, “social determinants of health”, “current management”, and “sub-Saharan Africa” from Jan 1, 2011, to June 15, 2021. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this paper.

improvement and long-term safety data in NAFLD are lacking.¹²⁵

Lifestyle modification, physical activity, and weight loss remain the mainstay of NAFLD management. However, these changes are challenging to put into practice and even more so to sustain. Due to various shared pathogenic mechanisms leading to the development of NAFLD and type 2 diabetes, anti-diabetic therapies are potential treatment options for the management of both disease states. Current data support the use of thiazolidinediones and GLP-1 agonists as the only anti-hyperglycaemic agents showing histological improvement of NASH. To effectively address and perhaps offset the consequences of NAFLD in sub-Saharan Africa, urgent attention is needed to ensure equitable access to therapies of proven clinical benefit, in addition to promoting the public health benefits of lifestyle modification.

Hypertension

Hypertension is a major risk factor promoting the development of NAFLD, occasionally independent of other risk factors. Good blood pressure control protects against NAFLD and the absence of hypertension mitigates against liver fibrosis in NAFLD.¹²⁶ Additionally, blood pressure control is crucial to offsetting the cardiovascular risks associated with NAFLD.

Dyslipidaemia

Multiple studies have shown the efficacy of lipid-lowering drugs in patients with NAFLD and NASH. These drugs include statins, fibrates, and ezetimibe. Statins are the most widely used and have known efficacy in reducing cardiovascular mortality in patients with coronary artery disease and type 2 diabetes.¹²⁷ Statins are safe and effective in patients with NAFLD or NASH and have no excess hepatotoxicity.¹²⁸ Furthermore, short-term treatment with statins can have beneficial effects on hepatic portal vein pressure, suggesting additional benefits in patients with advanced chronic liver disease or cirrhosis.¹²⁹

Bariatric surgery and obesity

Bariatric surgery is an effective treatment for obesity; with regard to NAFLD and NASH, it achieves histological

resolution of NASH through both weight loss-dependent and weight loss-independent mechanisms.¹³⁰ Paired liver biopsy studies and NAFLD activity scores show substantial improvements.¹³¹ In a prospective study of 109 patients with biopsy-proven NASH, 70 (85%) of 82 patients who had baseline and repeat liver biopsies had resolution 1 year after bariatric surgery, with a third of patients showing fibrosis regression according to Metavir scoring.¹³² Bariatric surgery in patients with NASH cirrhosis requires careful consideration given the incident risk of complications. However, the risk of death from cardiovascular causes, the leading cause of mortality in NASH, is reduced after bariatric surgery.¹³³ Surgical options include Roux-en-Y gastric bypass or sleeve gastrectomy; jejunioileal bypass is not recommended given its risk of liver decompensation.

Conclusions

In Africa, the estimated NAFLD prevalence of 13·5% for the general population is likely to be an underestimate, given the rising prevalence of obesity and type 2 diabetes, driven by the overlapping social challenges of food insecurity, nutritional transition, and associated increasing consumption of calorie-dense foods. The HIV infection burden, increasing access to antiretroviral therapy, and an ageing population are all contributing factors. Upscaling awareness and well designed epidemiological studies that screen for NAFLD in the general population as well as in high-risk groups are needed to assess the true prevalence and to guide public health policy in addressing this silent epidemic, which has long-term health-care costs and economic consequences for the region. Sub-Saharan Africa is possibly uniquely poised to proactively address the impending disease burden of NAFLD. The opportunity should not be missed.

Contributors

CWS conceived of the manuscript and developed the preliminary outline. All authors contributed to and provided region-specific perspectives; reviewed the full draft of the manuscript and subsequent revisions; and approved the final version for submission. MWS provided additional technical expertise.

Declaration of interests

We declare no competing interests.

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References

- 1 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73–84.
- 2 Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 11–20.
- 3 Sayiner M, Koenig A, Henry L, Younossi ZM. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in the United States and the rest of the world. *Clin Liver Dis* 2016; **20**: 205–14.

- 4 Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. *Lancet Gastroenterol Hepatol* 2021; **6**: 578–88.
- 5 Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology* 2019; **70**: 1913–27.
- 6 Younossi ZM. Non-alcoholic fatty liver disease - a global public health perspective. *J Hepatol* 2019; **70**: 531–44.
- 7 Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism* 2020; **111S**: 154170.
- 8 Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell* 2021; **184**: 2537–64.
- 9 Gouda HN, Charlson F, Sorsdahl K, et al. Burden of non-communicable diseases in sub-Saharan Africa, 1990–2017: results from the Global Burden of Disease Study 2017. *Lancet Glob Health* 2019; **7**: e1375–87.
- 10 Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**: 1747–57.
- 11 Ezzati M, Pearson-Stuttard J, Bennett JE, Mathers CD. Acting on non-communicable diseases in low- and middle-income tropical countries. *Nature* 2018; **559**: 507–16.
- 12 Jaspers Fajjer-Westerink H, Kengne AP, Meeks KAC, Agyemang C. Prevalence of metabolic syndrome in sub-Saharan Africa: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis* 2020; **30**: 547–65.
- 13 NCD Risk Factor Collaboration (NCD-RisC)—Africa Working Group. Trends in obesity and diabetes across Africa from 1980 to 2014: an analysis of pooled population-based studies. *Int J Epidemiol* 2017; **46**: 1421–32.
- 14 WHO. Obesity and overweight. June 9, 2021. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> (accessed Aug 23, 2021).
- 15 Muthuri SK, Francis CE, Wachira LJ, et al. Evidence of an overweight/obesity transition among school-aged children and youth in sub-Saharan Africa: a systematic review. *PLoS One* 2014; **9**: e92846.
- 16 International Diabetes Federation. IDF Diabetes Atlas: eighth edition. Brussels: International Diabetes Federation, 2017. https://diabetesatlas.org/upload/resources/previous/files/8/IDF_DA_8e-EN-final.pdf (accessed June 16, 2021).
- 17 Dessie G, Mulugeta H, Amare D, et al. A systematic analysis on prevalence and sub-regional distribution of undiagnosed diabetes mellitus among adults in African countries. *J Diabetes Metab Disord* 2020; **19**: 1931–41.
- 18 Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019; **71**: 793–801.
- 19 Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in sub-Saharan Africa: a systematic review and meta-analysis. *Hypertension* 2015; **65**: 291–98.
- 20 Noubiap JJ, Bigna JJ, Nansseu JR, et al. Prevalence of dyslipidaemia among adults in Africa: a systematic review and meta-analysis. *Lancet Glob Health* 2018; **6**: e998–1007.
- 21 Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. *BMC Nephrol* 2018; **19**: 125.
- 22 George JA, Brandenburg JT, Fabian J, et al. Kidney damage and associated risk factors in rural and urban sub-Saharan Africa (AW1-Gen): a cross-sectional population study. *Lancet Glob Health* 2019; **7**: e1632–43.
- 23 Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020; **73**: 202–09.
- 24 Cotter TG, Rinella M. Nonalcoholic fatty liver disease 2020: the state of the disease. *Gastroenterology* 2020; **158**: 1851–64.
- 25 Krawczyk M, Liebe R, Lammert F. Toward genetic prediction of nonalcoholic fatty liver disease trajectories: PNPLA3 and beyond. *Gastroenterology* 2020; **158**: 1865–80.e1.
- 26 Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). *Medicine (Baltimore)* 2018; **97**: e0214.
- 27 Hossain N, Afendy A, Stepanova M, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1224–29.
- 28 Caussy C, Soni M, Cui J, et al. Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis. *J Clin Invest* 2017; **127**: 2697–704.
- 29 Ekstedt M, Nasr P, Kechagias S. Natural history of NAFLD/NASH. *Curr Hepatol Rep* 2017; **16**: 391–97.
- 30 Li L, Liu DW, Yan HY, Wang ZY, Zhao SH, Wang B. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. *Obes Rev* 2016; **17**: 510–19.
- 31 Pang Q, Zhang JY, Song SD, et al. Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index. *World J Gastroenterol* 2015; **21**: 1650–62.
- 32 Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. *JHEP Rep* 2019; **1**: 329–41.
- 33 Younes R, Bugianesi E. NASH in lean individuals. *Semin Liver Dis* 2019; **39**: 86–95.
- 34 Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut* 2021; **70**: 962–69.
- 35 Cusi K, Sanyal AJ, Zhang S, et al. Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab* 2017; **19**: 1630–34.
- 36 Wu KT, Kuo PL, Su SB, et al. Nonalcoholic fatty liver disease severity is associated with the ratios of total cholesterol and triglycerides to high-density lipoprotein cholesterol. *J Clin Lipidol* 2016; **10**: 420–25.
- 37 Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; **67**: 328–57.
- 38 Jennison E, Byrne CD. The role of the gut microbiome and diet in the pathogenesis of non-alcoholic fatty liver disease. *Clin Mol Hepatol* 2021; **27**: 22–43.
- 39 Nettle D, Andrews C, Bateson M. Food insecurity as a driver of obesity in humans: the insurance hypothesis. *Behav Brain Sci* 2017; **40**: e105.
- 40 WHO. The double burden of malnutrition: policy brief. May 17, 2017. <https://www.who.int/publications/i/item/WHO-NMH-NHD-173> (accessed June 16, 2021).
- 41 Nkambule SJ, Moodley I, Kuupiel D, Mashamba-Thompson TP. Association between food insecurity and key metabolic risk factors for diet-sensitive non-communicable diseases in sub-Saharan Africa: a systematic review and meta-analysis. *Sci Rep* 2021; **11**: 5178.
- 42 Ge X, Zheng L, Wang M, Du Y, Jiang J. Prevalence trends in non-alcoholic fatty liver disease at the global, regional and national levels, 1990–2017: a population-based observational study. *BMJ Open* 2020; **10**: e036663.
- 43 Paruk IM, Pirie FJ, Motala AA. Non-alcoholic fatty liver disease in Africa: a hidden danger. *Glob Health Epidemiol Genom* 2019; **4**: e3.
- 44 Afolabi BI, Ibitoye BO, Ikem RT, Omisore AD, Idowu BM, Soyoye DO. The relationship between glycaemic control and non-alcoholic fatty liver disease in Nigerian type 2 diabetic patients. *J Natl Med Assoc* 2018; **110**: 256–64.
- 45 Olusanya TO, Lesi OA, Adeyomoye AA, Fasanmade OA. Non alcoholic fatty liver disease in a Nigerian population with type II diabetes mellitus. *Pan Afr Med J* 2016; **24**: 20.
- 46 Chukwurah N, Okonkwo U, Ihekwaba A. Comparative analysis of indices of the metabolic syndrome in patients with and without non-alcoholic fatty liver disease at a teaching hospital in Nnewi, South-East, Nigeria. *Asian J Med Sci* 2019; **10**: 40–45.
- 47 Onyekwere CA, Ogbera AO, Balogun BO. Non-alcoholic fatty liver disease and the metabolic syndrome in an urban hospital serving an African community. *Ann Hepatol* 2011; **10**: 119–24.
- 48 Ofori-Asenso R, Agyeman AA, Laar A, Boateng D. Overweight and obesity epidemic in Ghana—a systematic review and meta-analysis. *BMC Public Health* 2016; **16**: 1239.

- 49 Biritwum R, Gyapong J, Mensah G. The epidemiology of obesity in Ghana. *Ghana Med J* 2005; **39**: 82–85.
- 50 Setroame AM, Kormla Afrim P, Abaka-Yawson A, et al. Prevalence of metabolic syndrome and nonalcoholic fatty liver disease among premenopausal and postmenopausal women in Ho municipality: a cross-sectional study. *BioMed Res Int* 2020; **2020**: 2168381.
- 51 Ssentongo A, Ssentongo P, Keeney A, et al. Opportunistic screening for nonalcoholic fatty liver disease (NAFLD) in Ghana: a prospective study. *Curr Dev Nutr* 2020; **4** (suppl 2): 909.
- 52 Ntagirabiri R, Cikomola J, Baransaka E, et al. Hepatic steatosis and metabolic syndrome in black African adult: Burundi case. *J Afr Hepato Gastroenterol* 2014; **8**: 195–99.
- 53 Ahoui-Apendi C, Itoua-Ngaporo NA, Mongo-Onkouo A, et al. Hepatic steatosis in patients with metabolic syndrome at the Brazzaville University Hospital Center. *Open J Gastroenterol* 2020; **10**: 119–27.
- 54 Agyemang C, Boatema S, Frempong GA, de-Graft Aikins A. Obesity in sub-Saharan Africa. In: Ahima R, ed. *Metabolic syndrome*. Cham: Springer, 2015: 1–33. https://doi.org/10.1007/978-3-319-12125-3_5-1.
- 55 Sobngwi E, Mbanya JC, Unwin NC, et al. Exposure over the life course to an urban environment and its relation with obesity, diabetes, and hypertension in rural and urban Cameroon. *Int J Epidemiol* 2004; **33**: 769–76.
- 56 Zhou B, Lu Y, Hajifathalian K, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; **387**: 1513–30.
- 57 Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 766–81.
- 58 Global Health Data Exchange. Global Burden of Disease Study 2019 (GBD 2019) Socio-Demographic Index (SDI) 1950–2019. <http://ghdx.healthdata.org/record/ihme-data/gbd-2019-socio-demographic-index-sdi-1950-2019> (accessed Aug 1, 2021).
- 59 Kruger FC, Daniels C, Kidd M, et al. Non-alcoholic fatty liver disease (NAFLD) in the Western Cape: a descriptive analysis. *S Afr Med J* 2010; **100**: 168–71.
- 60 Macías J, Pineda JA, Real LM. Non-alcoholic fatty liver disease in HIV infection. *AIDS Rev* 2017; **19**: 35–46.
- 61 Hoffmann CJ, Hoffmann JD, Kensler C, et al. Tuberculosis and hepatic steatosis are prevalent liver pathology findings among HIV-infected patients in South Africa. *PLoS One* 2015; **10**: e0117813.
- 62 Sonderup MW, Wainwright H, Hall P, Hairwadzi H, Spearman CW. A clinicopathological cohort study of liver pathology in 301 patients with human immunodeficiency virus/acquired immune deficiency syndrome. *Hepatology* 2015; **61**: 1721–29.
- 63 Liu J, Ren ZH, Qiang H, et al. Trends in the incidence of diabetes mellitus: results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention. *BMC Public Health* 2020; **20**: 1415.
- 64 Sepanlou SG, Safiri S, Bisignano C, et al. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5**: 245–66.
- 65 Abebe SM, Berhane Y, Worku A, Assefa A. Diabetes mellitus in north west Ethiopia: a community based study. *BMC Public Health* 2014; **14**: 97.
- 66 Kassie AM, Abate BB, Kassaw MW. Prevalence of overweight/obesity among the adult population in Ethiopia: a systematic review and meta-analysis. *BMJ Open* 2020; **10**: e039200.
- 67 Abrha S, Shiferaw S, Ahmed KY. Overweight and obesity and its socio-demographic correlates among urban Ethiopian women: evidence from the 2011 EDHS. *BMC Public Health* 2016; **16**: 636.
- 68 Moges B, Amare B, Fantahun B, Kassu A. High prevalence of overweight, obesity, and hypertension with increased risk to cardiovascular disorders among adults in northwest Ethiopia: a cross sectional study. *BMC Cardiovasc Disord* 2014; **14**: 155.
- 69 Andargie M, Gebremariam K, Hailu T, Addisu A, Zereabruk K. Magnitude of overweight and obesity and associated factors among public and private secondary school adolescent students in Mekelle City, Tigray Region, Ethiopia, 2019: comparative cross-sectional study. *Diabetes Metab Syndr Obes* 2021; **14**: 901–15.
- 70 Tebekaw Y, Teller C, Colón-Ramos U. The burden of underweight and overweight among women in Addis Ababa, Ethiopia. *BMC Public Health* 2014; **14**: 1126.
- 71 Zawdie B, Tadesse S, Wolide AD, Nigatu TA, Bobasa EM. Non-alcoholic fatty liver disease and associated factors among type 2 diabetic patients in southwest Ethiopia. *Ethiop J Health Sci* 2018; **28**: 19–30.
- 72 Abdelmenan S, Banes A, Berhane Y, Abebe M, Wandall JH. Etiology of chronic liver disease in Ethiopia: a case control study with special reference to viral hepatitis and alcohol. *EC Gastroenterol Dig Syst* 2018; **5**: 120–28.
- 73 Fassil Shiferaw ML, Awoke Misganaw, et al. Non-communicable diseases in Ethiopia: disease burden, gaps in health care delivery and strategic directions. *Ethiop J Health Dev* 2018; **32**: 1–12.
- 74 Almobarak AO, Barakat S, Khalifa MH, Elhoweris MH, Elhassan TM, Ahmed MH. Non alcoholic fatty liver disease (NAFLD) in a Sudanese population: what is the prevalence and risk factors? *Arab J Gastroenterol* 2014; **15**: 12–15.
- 75 Almobarak AO, Barakat S, Suliman EA, et al. Prevalence of and predictive factors for nonalcoholic fatty liver disease in Sudanese individuals with type 2 diabetes: is metabolic syndrome the culprit? *Arab J Gastroenterol* 2015; **16**: 54–58.
- 76 Elmadhoun WM, Noor SK, Ibrahim AA, Bushara SO, Ahmed MH. Prevalence of diabetes mellitus and its risk factors in urban communities of north Sudan: population-based study. *J Diabetes* 2016; **8**: 839–46.
- 77 Noor SK, Bushara SO, Sulaiman AA, Elmadhoun WM, Ahmed MH. Undiagnosed diabetes mellitus in rural communities in Sudan: prevalence and risk factors. *East Mediterr Health J* 2015; **21**: 164–70.
- 78 Omuse G, Maina D, Hoffman M, et al. Metabolic syndrome and its predictors in an urban population in Kenya: a cross sectional study. *BMC Endocr Disord* 2017; **17**: 37.
- 79 The World Bank. Urban population in sub-Saharan Africa: 2020 revision. <https://data.worldbank.org/indicator/SP.URB.GROW?locations=ZG> (accessed Aug 8, 2021).
- 80 Steyn NP, McHiza ZJ. Obesity and the nutrition transition in Sub-Saharan Africa. *Ann N Y Acad Sci* 2014; **1311**: 88–101.
- 81 Vorster HH, Kruger A, Margetts BM. The nutrition transition in Africa: can it be steered into a more positive direction? *Nutrients* 2011; **3**: 429–41.
- 82 Roser M, Ritchie H. Food supply. 2013. Our World in Data. <https://ourworldindata.org/food-supply> (accessed June 16, 2021).
- 83 Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. *J Hepatol* 2009; **51**: 918–24.
- 84 Basu S, McKee M, Galea G, Stuckler D. Relationship of soft drink consumption to global overweight, obesity, and diabetes: a cross-national analysis of 75 countries. *Am J Public Health* 2013; **103**: 2071–77.
- 85 Okop KJ, Lambert EV, Alaba O, et al. Sugar-sweetened beverage intake and relative weight gain among South African adults living in resource-poor communities: longitudinal data from the STOP-SA study. *Int J Obes* 2019; **43**: 603–14.
- 86 Audain K, Levy L, Ellahi B. Sugar-sweetened beverage consumption in the early years and implications for type-2 diabetes: a sub-Saharan Africa context. *Proc Nutr Soc* 2019; **78**: 547–53.
- 87 Todoric J, Di Caro G, Reibe S, et al. Fructose stimulated de novo lipogenesis is promoted by inflammation. *Nat Metab* 2020; **2**: 1034–45.
- 88 Rector RS, Thyfault JP. Does physical inactivity cause nonalcoholic fatty liver disease? *J Appl Physiol* (1985) 2011; **111**: 1828–35.
- 89 Kistler KD, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. *Am J Gastroenterol* 2011; **106**: 460–68, quiz 469.
- 90 Orci LA, Gariani K, Oldani G, Delaune V, Morel P, Toso C. Exercise-based interventions for nonalcoholic fatty liver disease: a meta-analysis and meta-regression. *Clin Gastroenterol Hepatol* 2016; **14**: 1398–411.
- 91 Barr AL, Partap U, Young EH, et al. Sociodemographic inequities associated with participation in leisure-time physical activity in sub-Saharan Africa: an individual participant data meta-analysis. *BMC Public Health* 2020; **20**: 927.

- 92 Guerrero R, Vega GL, Grundy SM, Browning JD. Ethnic differences in hepatic steatosis: an insulin resistance paradox? *Hepatology* 2009; **49**: 791–801.
- 93 Caldwell SH, Harris DM, Patrie JT, Hespdenheide EE. Is NASH underdiagnosed among African Americans? *Am J Gastroenterol* 2002; **97**: 1496–500.
- 94 Trépo E, Valenti L. Update on NAFLD genetics: from new variants to the clinic. *J Hepatol* 2020; **72**: 1196–209.
- 95 Dongiovanni P, Romeo S, Valenti L. Genetic factors in the pathogenesis of nonalcoholic fatty liver and steatohepatitis. *BioMed Res Int* 2015; **2015**: 460190.
- 96 Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; **40**: 1461–65.
- 97 Naran NH, Haagensen M, Crowther NJ. Steatosis in South African women: how much and why? *PLoS One* 2018; **13**: e0191388.
- 98 Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology* 2011; **54**: 344–53.
- 99 Griswold MG, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018; **392**: 1015–35.
- 100 Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. *Hepatology* 2018; **67**: 2141–49.
- 101 Weng G, Dunn W. Effect of alcohol consumption on nonalcoholic fatty liver disease. *Transl Gastroenterol Hepatol* 2019; **4**: 70.
- 102 European Association for the Study of the Liver (EASL). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; **64**: 1388–402.
- 103 Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012; **55**: 885–904.
- 104 Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology* 2015; **149**: 367–78.
- 105 Koutoukidis DA, Jebb SA, Tomlinson JW, Cobbold JF, Aveyard P. Association of weight changes with changes in histological features and blood markers in non-alcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2021; published online April 2. <https://doi.org/10.1016/j.cgh.2021.03.047>.
- 106 Hashida R, Kawaguchi T, Bekki M, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: a systematic review. *J Hepatol* 2017; **66**: 142–52.
- 107 Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol* 2017; **67**: 829–46.
- 108 Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362**: 1675–85.
- 109 Vadarlis A, Antza C, Bakaloudi DR, et al. Systematic review with meta-analysis: the effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2021; **36**: 311–19.
- 110 Vilar-Gomez E, Vuppalanchi R, Gawrieh S, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. *Hepatology* 2020; **71**: 495–509.
- 111 Pu R, Shi D, Gan T, et al. Effects of metformin in obesity treatment in different populations: a meta-analysis. *Ther Adv Endocrinol Metab* 2020; **11**: 204.201.8820926000.
- 112 Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. *Gut* 2013; **62**: 606–15.
- 113 Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care* 2012; **35**: 723–30.
- 114 Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med* 2017; **177**: 633–40.
- 115 Mahady SE, Webster AC, Walker S, Sanyal A, George J. The role of thiazolidinediones in non-alcoholic steatohepatitis—a systematic review and meta analysis. *J Hepatol* 2011; **55**: 1383–90.
- 116 Rizos CV, Elisaf MS, Mikhailidis DP, Liberopoulos EN. How safe is the use of thiazolidinediones in clinical practice? *Expert Opin Drug Saf* 2009; **8**: 15–32.
- 117 Duan CM, Wan TF, Wang Y, Yang QW. Cardiovascular outcomes of liraglutide in patients with type 2 diabetes: a systematic review and meta-analysis. *Medicine (Baltimore)* 2019; **98**: e17860.
- 118 Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016; **387**: 679–90.
- 119 Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021; **384**: 1113–24.
- 120 Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021; **384**: 989–1002.
- 121 Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021; **397**: 971–84.
- 122 Kawakubo M, Tanaka M, Ochi K, et al. Dipeptidyl peptidase-4 inhibition prevents nonalcoholic steatohepatitis-associated liver fibrosis and tumor development in mice independently of its anti-diabetic effects. *Sci Rep* 2020; **10**: 983.
- 123 Cui J, Philo L, Nguyen P, et al. Sitagliptin vs. placebo for non-alcoholic fatty liver disease: a randomized controlled trial. *J Hepatol* 2016; **65**: 369–76.
- 124 Komiya C, Tsuchiya K, Shiba K, et al. Ipragliflozin improves hepatic steatosis in obese mice and liver dysfunction in type 2 diabetic patients irrespective of body weight reduction. *PLoS One* 2016; **11**: e0151511.
- 125 Scheen AJ. Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: a common comorbidity associated with severe complications. *Diabetes Metab* 2019; **45**: 213–23.
- 126 Aneni EC, Oni ET, Martin SS, et al. Blood pressure is associated with the presence and severity of nonalcoholic fatty liver disease across the spectrum of cardiometabolic risk. *J Hypertens* 2015; **33**: 1207–14.
- 127 Iqbal U, Perumpail BJ, John N, et al. Judicious use of lipid lowering agents in the management of NAFLD. *Diseases* 2018; **6**: 87.
- 128 Pastori D, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis* 2015; **47**: 4–11.
- 129 Gu Y, Yang X, Liang H, Li D. Comprehensive evaluation of effects and safety of statin on the progression of liver cirrhosis: a systematic review and meta-analysis. *BMC Gastroenterol* 2019; **19**: 231.
- 130 Perysinakis I, Pappis HC, Margaris E. Current controversies in metabolic surgery for nonalcoholic fatty liver disease. *Obes Surg* 2019; **29**: 1058–67.
- 131 Mathurin P, Hollebecque A, Arnalsteen L, et al. Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. *Gastroenterology* 2009; **137**: 532–40.
- 132 Lassailly G, Caiazzo R, Buob D, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. *Gastroenterology* 2015; **149**: 379–88.
- 133 Aminian A, Zajichek A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. *JAMA* 2019; **322**: 1271–82.

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